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UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

GILEAD SCIENCES, INC.,

Plaintiff and Counterdefendant,

v.

MERCK & CO., INC. (Defendant only), MERCK SHARP & DOHME CORP. and ISIS PHARMACEUTICALS, INC.,

Defendants and Counterclaimants.

Case No. 5:13-cv-04057-BLF

DEFENDANTS' REPLY CLAIM CONSTRUCTION BRIEF

Date: April 3, 2015
Time: 9:00 a.m.
Ctrm: 3, 5th Floor
Judge: Honorable Beth Labson Freeman

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INTRODUCTION

Merck & Co., Inc., Merck Sharp & Dohme Corp., and Isis Pharmaceuticals, Inc., (collectively, "Merck") respectfully submit this reply brief in support of their proposed constructions of the terms "compound" and "administering" as used in the asserted claims of U.S. Patent Nos. 7,105,499 ("the '499 Patent") and 8,481,712 ("the '712 Patent") (collectively, the "patents-in-suit" or "Merck Patents"), and in reply to the Responsive Claim Construction Brief (ECF No. 96) filed by Gilead ("Gilead Br.").

Gilead's positions are inconsistent with well-settled principles of claim construction. Moreover, Gilead relies on a selective reading of the patents-in-suit that ignores key teachings of the specification that contradict its position. Contrary to Gilead's contention, the specification expressly uses the term "compound" to refer to compounds that are synthesized in the laboratory ***and*** to compounds that are formed in the body by metabolism. The claimed compounds are defined by their chemical composition and structure, through the recitation of chemical formulas, and not by the manner in which the compounds are made. There is no "clear disavowal of claim scope," as would be required to justify deviating from established meaning of the term "compound" as used in the art of the patents-in-suit.

With respect to the term "administering," the patents-in-suit set forth an explicit definition, which has controlling force. Gilead's construction deviates from the patentees' definition of "administering" by seeking to import extraneous limitations derived from the working examples of the specification, which is contrary to settled principles of claim construction.

Merck's constructions are grounded in the intrinsic record and are true to the language of the claims and controlling precedent. Accordingly, the Court should reject Gilead's proposed constructions and adopt those proposed by Merck for each disputed term.

ARGUMENT

I. THE PROPER CONSTRUCTION OF "COMPOUND"

It is well established that claim terms generally receive their ordinary and customary meaning as understood by a person of ordinary skill in the art except when a patentee (1) sets out a definition and acts as his own lexicographer, or (2) disavows the full scope of a claim term either in the specification or during prosecution. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc); *see also* Gilead Br. at 5-6; Merck's Opening Claim Construction Br. (ECF No. 91) at 4, 11 ("Merck Br.").

Gilead does not dispute that Merck has accurately stated the ordinary and customary meaning of the term "compound," as used in the art of the patents-in-suit, namely: "a substance that consists of two or more chemical elements in union." Nor does Gilead dispute that the claims specify the compounds that are claimed (or whose use is claimed) by their chemical composition and structure. Nevertheless, Gilead contends that this term should be construed, contrary to its ordinary meaning, as referring only to compounds that have been made synthetically, as distinct from compounds produced by metabolism in the body. As shown below, Gilead misreads the claim language, ignores teachings of the patents-in-suit that contradict its position, and misapplies relevant precedent.

A. The Language of the Claims Does Not Support Gilead's Construction

Gilead misreads the claims when it contends that the phrase "pharmaceutically acceptable salts" requires the term "compound" to be limited to a compound that is synthetically produced. Gilead Br. at 7-8, 15-16. The claims define two alternative ways of practicing the invention: (i) by means of specified compounds, or (ii) by means of pharmaceutically acceptable salts of specified compounds. Even if the second alternative requires the use of salts that are prepared synthetically, it does not follow that the first alternative requires the use of compounds that are synthetically produced.

The claims of the '712 Patent use the disjunctive form ("or") when they recite: "[a] compound having the formula [specified in the claim] ***or*** *a pharmaceutically acceptable salt* thereof . . . ." '712 Patent, cols. 143-46 (emphasis added). Claim 1 of the '499 Patent likewise uses the disjunctive form when it recites administering a "compound of [the] structural formula [specified in the claim] ***or*** *a pharmaceutically acceptable salt or acyl derivatives* thereof . . . ." '499 Patent, cols. 137-38 (emphasis added). By using the conjunction "or," the claims define alternative ways of practicing the claimed invention. Gilead's argument, however, does not give effect to the conjunction — "***or***" — that separates these alternatives in the claims. This is improper. *Cf. Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so.").

The established art-recognized meaning of "compound" readily accommodates both alternatives by including compounds that have the structure defined by the claims, regardless of how they were made. When the claimed invention is practiced by means of the compounds defined in the claims, the

compounds in question can be artificially synthesized (*e.g.*, in the laboratory) or produced in the body of a patient (*e.g.*, by metabolic conversion of a prodrug). The Court should reject Gilead's invitation to rewrite the claims by ignoring the disjunctive effect of the conjunction "***or***," as contrary to established principles of claim construction. *See, e.g., K–2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364 (Fed. Cir. 1999) ("Courts do not rewrite claims; instead, [they] give effect to the terms chosen by the patentee).

Nor does claim 2 of the '499 Patent support a narrow construction of "compound," as Gilead contends, by its recitation that the compound of claim 1 is administered "in combination with" a second therapeutic agent. *See* Gilead Br. at 8. The parties have stipulated that "in combination with" means: "together with, whether ***given separately at different times*** during the course of therapy ***or concurrently*** in divided or single dosage forms." Joint Claim Construction and Prehearing Statement (ECF No. 86) at 2 (emphasis added); *see also* '499 Patent, col. 32, lines 32-36 (same). Nothing about claim 2 requires a narrow construction of "compound." On the contrary, claim 2 can be practiced by combination therapy that comprises (i) administering a prodrug (such as sofosbuvir) that is metabolized in the body to produce mono-, di- and triphosphate compounds covered by the asserted claims of the patents-in-suit, and (ii) providing the second therapeutic agent "separately at different times" during the same course of therapy, or concurrently, in a separate dosage form. That is exactly what Gilead's label induces patients to do by instructing that "SOVALDI should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for treatment of CHC [chronic hepatitis C] in adults." SOVALDI Prescribing Information § 2.1, Flanagan Decl., Ex. B (ECF No. 96-3). Combination therapy, as defined in the '499 Patent, does not require the compound of the invention to be given in a combined dosage form with another agent. It can be – and is – practiced by providing the patient with a prodrug that is metabolized to a claimed compound (SOVALDI) as well as a second dosage form containing ribavirin, and often a third dosage form containing pegylated interferon.

B. The Disclosure of the Patents-in-Suit Does Not Support Gilead's Construction

Gilead contends that "the written description [of the patents-in-suit] ***never*** refers to compounds or metabolites generated in vivo by the body." *See* Gilead Br., at 9 (emphasis in original); *see also id.* at 2 ("The claims and written description ***never***—in words or figures—describe compounds produced by the body.") (emphasis in original). Gilead's assertion is simply wrong.

The patents-in-suit teach two ways of practicing the disclosed invention. First, the invention can be practiced by "providing *a compound of the invention* . . . to the individual in need." '499 Patent, col. 32, lines 6-8 (emphasis added). In this mode of practicing the invention, the claimed compound ("compound of the invention") is synthesized and then given ("provid[ed]") to the patient. However, the patents-in-suit also teach a second mode of practicing the invention, namely, by "providing . . . *a prodrug of a compound of the invention* to the individual in need." *Id* (emphasis added). By definition, a "prodrug" is a precursor that must be transformed (metabolized) in the body into an active therapeutic compound. *See* Merck Br. at 3 ("[P]rodrugs are 'derivatives of a drug molecule *that require a transformation within the body* to release the active drug.'") (quoting V.J. Stella et al., Prodrugs. Do They Have Advantages in Clinical Practice?, 29 Drugs 455, 455 (1985), Rabinowitz Decl., Ex. 4 (ECF No. 91-5) (emphasis added); *accord* Gilead Br. at 1 (stating that sofosbuvir is "a particular prodrug—it is inactive until transformed by enzymes in the body to an active form"). By teaching that a patient may be treated with *a prodrug of a compound* of the invention, the patents-in-suit expressly disclose, to a person of ordinary skill in the art, that the therapeutic "compound" will be formed by metabolism of the prodrug. To put it another way, the prefix "pro" in "prodrug" means "precursor." A prodrug serves as a delivery vehicle for the compound into which it is converted and has no other purpose than to be transformed into the active therapeutic compound. It would be nonsensical to refer to a prodrug "without reference to in vivo transformations," as Gilead proposes. *See* Gilead Br. at 14. On the contrary, the very name "prodrug" refers to a compound that is transformed *in vivo* to another compound. If that were not the case, the "prodrug" would simply be a "drug."

Gilead disregards the teachings discussed above and argues that the Examples set forth in the patents-in-suit limit the claimed subject matter to synthetically produced compounds because the Examples illustrate how to synthesize compounds encompassed by the claims. Gilead Br. at 9-10. That argument is flawed in law and in fact.

As a matter of law, the Federal Circuit has repeatedly made clear that the working examples by which the inventors illustrate their invention may not be used to limit the claims. Absent a clear disclaimer, "claim terms must be given their plain and ordinary meaning to one of skilled in the art." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1367 (Fed. Cir. 2012) (citing *Phillips*, 415

F.3d at 1316); *see also Home Diagnostic, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004) ("Absent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language.").

The Federal Circuit has specifically rejected the proposition that the embodiments used to exemplify the invention can be used to limit the claims. "The standard for disavowal of claim scope is . . . exacting." *Thorner*, 669 F.3d at 1366. "***It is . . . not enough that the only embodiments, or all of the embodiments, contain a particular limitation***." *Id.* (emphasis added). "[Courts] do not read limitations from the specification into claims; [courts] do not redefine words." *Id.*

The specifications of the patents-in-suit reinforce this legal rule by expressly stating that the examples shall *not* be regarded as limiting. Gilead quotes from the following passage in the specifications of the patents-in-suit, but has cropped the quote by omitting the highlighted sentence:

> The examples below provide citations to literature publications, which contain details for the preparation of final compounds or intermediates employed in the preparation of final compounds of the present invention. The nucleoside compounds of the present invention were prepared according to procedures detailed in the following examples. ***The examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed***. Those skilled in the art of nucleoside and nucleotide synthesis will readily appreciate that known variations of the conditions and processes of the following preparative procedures can be used to prepare these and other compounds of the present invention.

'499 Patent, col 40, lines 28-41 (emphasis added); *cf.* Gilead Br. at 18.

As the Federal Circuit has explained, "[t]o avoid importing limitations from the specification into the claims, it is important to keep in mind that the purposes of the specification are to teach and enable those of skill in the art to make and use the invention and to provide a best mode for doing so." *Phillips*, 415 F.3d at 1323. The specification of the patents-in-suit included examples for these very purposes, and not by way of limitation, and the patentees took care to say so.

Moreover, Gilead also overlooks that the specification of the patents-in-suit provides additional teachings about *in vivo* transformation through documents that are incorporated by reference. *See SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1366 (Fed. Cir. 2012) ("[A] document incorporated by reference becomes effectively part of the host document as if it were explicitly contained therein.") (internal quotation marks and citation omitted); *Chiron Corp. v. SourceCF Inc.*, 431 F. Supp. 2d 1019,

1031 n.5 (N.D. Cal. 2006) ("Any incorporated material must be considered in interpreting the host document. When a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein. Indeed, the whole point of incorporation by reference is to make the material part of the patent . . . . ") (citation omitted).

Example 72, cited on page 13 of Gilead's brief, is concerned with prodrugs and incorporates by reference several documents in this regard, including Carston R. Wagner et al., Pronucleotides: Toward the In Vivo Delivery of Antiviral and Anticancer Nucleotides, 20 Med. Res. Rev. 417 (2000) ("Wagner") (Rabinowitz II Decl., Ex. A)[1]. *See* '499 Patent col. 77, lines 60-63 (incorporating Wagner "in its entirety"). Wagner teaches about the use of prodrugs (also referred to as "pronucleotides") for *in vivo* delivery of, *inter alia*, antiviral nucleotides. As Wagner explains, such a prodrug must be "intracellularly convertible to the corresponding nucleotide" (*i.e.*, it must undergo metabolism to the active therapeutic compound). Wagner at 417 (Abstract). By way of background, Wagner explains that naturally occurring nucleosides are successively converted, by a process called "phosphorylation," into mono-, di- and tri-phosphate forms, and that the same is true of prodrugs "since they must be phosphorylated intracellularly in order to be biologically active." *Id*. at 417-18; *see also id.* at 425, fig. 6 (depicting metabolism of a prodrug into a phosphorylated nucleotide). *Contra* Gilead Br. at 9 (contending that "the written description never refers to compounds or metabolites generated in vivo by the body.") (emphasis omitted). Indeed, Wagner even discloses the preparation of "phosphoramidate" prodrugs. *See* Wagner at 435; *cf.* Gilead Br. at 1 (admitting that "sofosbuvir uses a chemical structure called a 'phosphoramidate' to ensure that the correct active molecule is delivered to liver cells to stop replication of the HCV virus.").

Nor is Wagner the only means by which the patents-in-suit teach that a prodrug must be metabolized to a triphosphate derivative. The specification incorporates an additional reference that teaches as follows:

[1] Declaration of Stephen S. Rabinowitz in Support of Defendants' Reply Claim Construction Brief (submitted herewith).

> Certain compounds, such as nucleoside derivatives or analogs, are active agents that are administered in non-phosphorylated form, but are phosphorylated *in vivo in the form of metabolic monophosphate or triphosphate to become active.*

U.S. Patent No. 5,770,725, col. 1, lines 29-33, Rabinowitz II Decl., Ex. B (emphasis added); '499 Patent, col. 77, lines 64-67 (incorporating this patent in its entirety). As a matter of law, these incorporated documents are part of the disclosure of the patents-in-suit and must be given effect. *SanDisk*, 695 F.3d at 1366.

Gilead's responsive brief ignores these teachings and focuses instead on one passage where the specification states that "*[t]he compounds of the present invention* ***may*** *be administered in the form of a pharmaceutically acceptable salt.*" Gilead Br. at 7-8 (emphasis added). But Gilead misinterprets this sentence. Use of the word "***may***" in this sentence is permissive and conveys that "pharmaceutically acceptable salts" are but one possible means of practicing the invention. *See, e.g.*, *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1378 (Fed. Cir. 2003) ("'Can' and 'may' are commonly used by patentees to show that a limitation is permissive."); *Enova Tech. Corp. v. Initio Corp.*, No. 10-04-LPS, 2012 WL 6738398, at *4 (D. Del. Dec. 28, 2012) (rejecting defendants' construction because it "would limit the claims to such a single, integrated 'unit,' which is unwarranted given the permissive 'may' language in the specification . . . .").

Contrary to Gilead's proposed construction, a person of ordinary skill in the art would understand that the claimed compounds "may" be administered in the form of pharmaceutically acceptable salts or, in the alternative, "may" be formed *in vivo* from a prodrug that is metabolized to a claimed compound. As shown above, the patents-in-suit disclose that the invention can be implemented by providing a prodrug that is converted into a compound of the invention, and describe how prodrugs undergo metabolism in the body to produce active compounds, including tri-phosphate analogs.

C. Applicable Precedent Does Not Support Gilead's Construction

Certain principles of claim construction are fundamental. First, when construing claims, "the court must always read the claims in view of the full specification." *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1373 (Fed. Cir. 2005) (citation omitted). Second, it is a "cardinal sin[]" to depart from the plain meaning of a term by reading into the claim a limitation from the specification. *Phillips*, 415 F.3d at 1320 (citation omitted). Third, the requirements for a disclaimer are exacting—there must be

a "clear and unmistakable disavowal" in order to justify narrowing the scope of a claim. *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1120 (Fed. Cir. 2004).

As discussed above, Gilead's assertion that the plain language of the claims refers to only synthetically produced compounds is insupportable. And as shown above, the written description of the patents-in-suit is not limited to synthetically produced compounds, as Gilead contends.

Gilead's reliance on *Marion Merrell Dow Inc. v. Baker Norton Pharmaceuticals, Inc.*, 948 F. Supp. 1050 (S.D. Fla. 1996), to support its construction of "compound" is misplaced. The construction adopted by the *Marion* court did not turn chiefly on the recitation of "pharmaceutically acceptable salt," as Gilead's discussion of this case implies. *See* Gilead Br. at 8. In *Marion*, the patent specification "contain[ed] no reference whatsoever to [the compound] TAM created in vivo by metabolism." 948 F. Supp. at 1055. By contrast, the patents-in-suit here expressly teach the use of a prodrug that is metabolized into a compound of the invention. The *Marion* Court also focused on dependent claims directed towards a pharmaceutical composition in tablet or unit dosage forms. *Id*. at 1054. The patents-in-suit here do not include any such claims. In *Marion*, the patentee disclaimed metabolically produced compounds during prosecution by "adopt[ing] the examiner's interpretation of 'compound' as limited to that formed by synthetic means." *Id*. at 1055. There has been no such disclaimer during prosecution of the patents-in-suit here. Accordingly, *Marion* is inapplicable here.

Gilead's reliance on *In re Omeprazole Patent Litigation*, No. MDL 1291, 2001 WL 585534 (S.D.N.Y. May 31, 2001), is likewise misplaced. In *In re Omeprazole*, the claimed compound was ***required*** to be "a pharmaceutically acceptable anion." *Id*. at *4 (explaining that claim 1 of U.S. Patent No. 4,636,499 depicts a general formula that includes a component X in which "the X shown in the drawing represents 'a pharmaceutically acceptable anion'"). Given that claim language, the court found that "[b]y describing the invention in terms of an anion chosen pursuant to pharmaceutical standards, the inventors" sought a formulation "available in only the synthetic context . . . ." *Id*. at *4. Moreover, in *In re Omeprazole*, the patentee "admit[ted] that some of the anions listed . . . did not occur in vivo." *Id*. at *5. In the patents-in-suit here, the claims contain no such requirement and the inventors made no such admission, but on the contrary taught the use of a prodrug that is converted in vivo into a compound of the invention. Accordingly, the reasoning of the court in *In re Omeprazole* is inapplicable here.

Unlike *Marion* and *In re Omeprazole*, the patents-in-suit disclose compounds generated *in vivo* from a prodrug. The precedents Merck cites (*Aventis* and *Ortho-McNeil*) are consistent with Merck's proposed constructions and apply the principles set forth in *Phillips* by not departing from the ordinary meaning of the disputed term "compound" when presented with similar claims-at-issue. *See, e.g.*, *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, No. 2:05CV421, 2006 WL 1314413, at *4 (E.D. Va. May 11, 2006) (construing "compound" to mean "a 'structure' made up of specific chemical constituents" where "the plain language of claim 1 uses the term 'compound' like it uses the word 'formula'—as a fairly broad term"); *Ortho-McNeil Pharm. v. Mylan Labs*, 348 F. Supp. 2d 713, 726-28 (N.D.W.V. 2004) (adopting the ordinary meaning of "compound" where the claims recited a compound defined by structural formula and stating: "Under a standard dictionary definition, 'compound' means 'a chemically distinct substance formed by union of two or more ingredients (as elements) . . . .'") (citation omitted).

Gilead has failed to meet its heavy burden of showing a clear and unmistakable disavowal. *Thorner*, 669 F.3d at 1366. There is thus no basis for reading Gilead's proposed limitations into the claims and doing so would be inconsistent with the plain language of the claims, the intrinsic record, and applicable precedent. The Court should reject Gilead's construction, and adopt Merck's construction of the claim term "compound."

II. THE PROPER CONSTRUCTION OF "ADMINISTERING"

The legal and factual flaws identified above also infect Gilead's arguments in support of its proposed construction of the term "administering" as used in claim 1 of the '499 Patent. Once again, Gilead's responsive brief misreads the claim language, ignores teachings of the patents-in-suit that contradict Gilead's position, and misapplies relevant precedent.

A. The Language of the Claims Does Not Support Gilead's Construction

The term "administering" is expressly defined in the specification of the '499 Patent and is assigned the following meaning: "providing a compound of the invention or a prodrug of a compound of the invention to the individual in need." '499 Patent, col. 32, lines 5-8. As shown above, a "prodrug of a compound of the invention" refers to and means a prodrug *that converts in vivo* into a compound of the invention. Since the defined term "administering" appears in the claims of the '499 Patent, Gilead is

wrong when it asserts that there is "no language in the claims that instructs the skilled artisan to take into account in vivo transformations of the compounds provided to patients . . . ." Gilead Br. at 15. Moreover, as shown above, the claim language does not support Gilead's narrow construction by reciting *in the alternative* that the claimed method can be practiced by administering a structurally defined compound ***or*** a pharmaceutically acceptable salt or acyl derivative. Nor, for the reasons set forth above, does the recitation of "in combination with" in claim 2 of the '499 Patent support Gilead's construction. On the contrary, by using the defined term "administering," the claim language supports the construction proposed by Merck.

B. The Disclosure of the '499 Patent Does Not Support Gilead's Construction

As with "compound," Gilead relies on a selective and inaccurate reading of the specification in support of its proposed construction of "administering."

First, Gilead parses the word "providing" as meaning "giving to," "supplying" or "making available" in order to conclude that "providing stops when the patient receives *the compound*." Gilead Br. at 16 (emphasis added). But Gilead ignores what happens when a patient receives *a prodrug* in accordance with the teachings of the specification. As explained above, by reference to the specification, the prodrug is metabolized *in vivo* to form mono-, di-, and tri-phosphate analogs. The ability to undergo metabolism in the body is the very hallmark of a prodrug, and distinguishes prodrugs from mere drugs. The phrase "prodrug *of a compound* of the invention" means a prodrug that is metabolized in the body to yield one or more of the claimed compounds.

Gilead inappropriately relies on other portions of the specification, which explain that "[t]he compounds of the present invention ***may*** be administered in the form of a pharmaceutically acceptable salt" and which describe "various dosage forms that ***can*** be administered . . ." Gilead Br. at 17 (emphasis added). But these disclosures merely identify alternative ways of practicing the invention, and do not gainsay the express teachings of the specification that the invention can be practiced by providing a prodrug of a compound of the invention – such as sofosbuvir (which Gilead is selling as SOVALDI).

Gilead also contends that the '499 Patent uses the term "administering" consistent with its ordinary meaning. Gilead Br. at 16-17 (citing '499 Patent col. 32, lines 36-39). But the cited passage does not support Gilead's position. The cited passage teaches combination therapy in which a compound

of the invention is "administered" in combination with other therapeutic agents. As shown above, combination therapy includes *administering a prodrug* (such as sofosbuvir) that is metabolized to produce a compound of the invention, and providing the second therapeutic agent separately at different times during the course of therapy. The teaching relied on by Gilead is fully consistent with the definition of "administering" set forth in the preceding paragraph of the '499 Patent. *See* '499 Patent, col. 32, lines 5-8.

Accordingly, the entirety of the specification, as well as the claim language, is in accordance with the express definition of "administering" set forth in the '499 Patent. Where, as here, the specification provides an express definition for a claim term, which is supported by the intrinsic evidence, courts construe the term as it is defined. *See, e.g., 3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1374 (Fed. Cir. 2003).

C. Gilead's Extrinsic Evidence Cannot Be Used to Change the Express Definition of "Administering" Provided in the Specification

Gilead's reliance on extrinsic evidence to contradict the specification definition of "administering" is flawed in law and in fact.

As a factual matter, the extrinsic sources cited by Gilead do not support its position. Gilead relies on the Merck Manual's definition of "pharmacokinetics" and its discussion of "Drug Input and Disposition" for the proposition that "metabolites form only *after* a drug is administered" and that "administration" (in its conventional sense) can be distinguished "from the other steps in a drug's journey through the body." Gilead Br. at 18-19. But none of the cited passages addresses the specific definition of "administering" set forth in the '499 Patent, and none of them discusses what happens when the medicament in question is a prodrug. Indeed, the Merck Manual recognizes that metabolism must be taken into account, even for drugs that are not prodrugs. *See* Merck Manual at GILEAD00001000, Flanagan Decl., Ex. F (ECF No. 96-7) ("For drugs with an active metabolite, the therapeutic consequence of first-pass *metabolism* depends on the contributions of the drug *and the metabolite* to the desired and undesired effects.") (emphasis added).

Gilead's cited references are irrelevant to how "administering" should be construed in light of the express definition set forth in the specification and the additional teachings about prodrugs in documents

that are incorporated by reference into the specification of the '499 Patent.

Moreover, as a matter of law, these extrinsic references cannot overcome the definition in the specification. "Because the specification clearly and unambiguously define[s] the disputed term in the claim, reliance on . . . extrinsic evidence [is] unnecessary and, hence, legally incorrect." *Vitronics Corp. v. Conceptronic, Inc*., 90 F.3d 1576, 1585 (Fed. Cir. 1996) ("[R]egardless of how those skilled in the art would interpret a term . . . [courts] must give it the meaning indicated by the patentee[.]"). Since the inventors "expressly acted as [their] own lexicographer by providing a definition of [administering] in the specification, the definition in the specification controls the meaning of [administering], regardless of any potential conflict with the term's ordinary meaning . . . ." *3M Innovative*, 350 F.3d at 1374; *see also Boss Control, Inc. v. Bombardier Inc.*, 410 F.3d 1372, 1378 (Fed. Cir. 2005) ("Neither the dictionary definition nor the prosecution history, however, overcomes the particular meaning of 'interrupt' clearly set forth in the specification. . . . [W]hile it is true that during prosecution the applicants twice used the phrase 'cut off' interchangeably with the term 'interrupt,' this usage does not operate to erase the clear definition of 'interrupt' found in the specification . . . .").

D. The Prosecution History Does Not Support Gilead's Construction

Gilead cites to an amendment as supposedly supporting its construction of "administering." Gilead Br. at 22-23. In the amendment, the phrase "ester prodrug" was replaced by the phrase "acyl derivative." The prosecution history does not reveal the reason for the amendment, which was made by the Examiner (with authorization from the applicants' attorney), concurrently with allowing the claims. *See* Excerpt from '499 Prosecution History (Flanagan Decl., Ex. G) at MERCK0005818.

This sparse record provides no basis whatsoever for Gilead's assertion that the change in claim language was "a clear disclaimer of any kind of prodrug in favor of just those that were both described and expressly claimed." Gilead Br. at 23. Gilead's speculations to that effect are not supported by any exchanges between the applicant and the Examiner in the prosecution history. On the contrary, it was unnecessary and redundant to recite "or ester prodrug" in light of the specification's express definition of "administering," which includes providing a prodrug (not limited to an ester prodrug) of a compound of the invention. Accordingly, the omission of "or ester prodrug" did not narrow the scope of the claims. As the Federal Circuit has explained, in the very case cited by Gilead: "[w]e have, however, declined to

apply the doctrine of prosecution disclaimer where the alleged disavowal of claim scope is ambiguous." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324, 1325 (Fed. Cir. 2003 ("To balance the importance of public notice and the right of patentees to seek broad patent coverage, we have thus consistently rejected prosecution statements too vague or ambiguous to qualify as a disavowal of claim scope."). The prosecution history does not support deviating from the express definition of "administering" that is set forth in the specification.

E. The Cases Cited by Gilead Do Not Support Its Construction

Gilead cites *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 957-58 (Fed. Cir. 2014), as supposed support for deviating from the specification's express definition of "administering." Gilead Br. at 18. But that case actually supports Merck's claim construction. In *Allergan*, the issue was not *whether to apply* the specification's definition of the term in question, but rather how to interpret the express definition set forth in the specification, which was ambiguous. *Id.* On reviewing "the patentee's own lexicography in light of the whole specification," the *Allergan* court concluded that the definition set forth in the specification was broad and declined to depart from it by adopting a narrower construction, as Gilead's proposes to do here. *Id.* at 958. Notably, the *Allergan* court rejected the accused infringer's argument that the disputed term should be given its plain and ordinary meaning where the specification expressly defined the term to have a broader meaning. *Id.* at 957-958.

Gilead also relies on *Trading Technologies International, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1353 (Fed. Cir. 2010). Gilead Br. at 18. But Gilead misreads *Trading Technologies* as standing for the proposition that "a patent's alleged definition of a claim term is not necessarily the correct construction; the entire intrinsic record must be reviewed to arrive at the correct construction." Gilead Br. at 18. In *Trading Technologies*, the specification set forth a definition of the term "static" that was incomplete. 595 F.3d at 1353 (reciting the definition, which included the phrase "discussed in detail later"). In view of that language, the court concluded that "that definition expressly promises to discuss 'a recentering command . . . later' in the specification" and accordingly examined the remainder of the specification for that further disclosure. *Id.* The court also gave effect to an exchange with the Examiner in which the applicants expressly "jettisoned the word 'normally' during prosecution." *Id.* at 1354. Here, the specification's definition of "administering" is not incomplete, and the applicants did not "jettison" any

portion of that definition. Accordingly, *Trading Technologies* is inapplicable.

Finally, Gilead relies on *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) for the proposition that the Court should adopt Gilead's proposed construction of "administering" in order to save the claims of the '499 Patent from supposed invalidity for indefiniteness. Gilead Br. at 24. This is a red herring. Merck will vigorously deny and dispute any allegation by Gilead that these claims are invalid, a proposition that Gilead would have to prove by clear and convincing evidence. There is no warrant for Gilead to rely on unsubstantiated *allegations* of invalidity in order to narrow the claims of the '499 Patent. The Federal Circuit has specifically disapproved this exact tactic. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 911 (Fed. Cir. 2004) (distinguishing *Rhine* and holding that "unless the court concludes, after applying all the available tools of claim construction, that the claim is still ambiguous, the axiom regarding the construction to preserve the validity of the claim does not apply"); *accord Phillips*, 415 F.3d at 1327 ("While we have acknowledged the maxim that claims should be construed to preserve their validity, we have not applied that principle broadly, and we have certainly not endorsed a regime in which validity analysis is a regular component of claim construction. Instead, we have limited the maxim to cases in which the court concludes, after applying all the available tools of claim construction, that the claim is still ambiguous.") (internal quotation marks and citation omitted).

CONCLUSION

For the reasons discussed above, Merck respectfully requests that the Court adopt its proposed constructions.

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